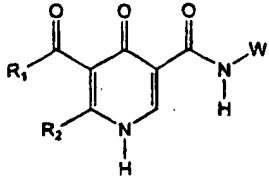


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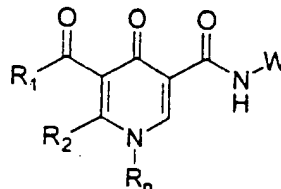


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<p>(51) International Patent Classification ⁶ : C07D 213/82, 215/54, 417/12, A61K 31/455</p>	<p>A1</p>	<p>(11) International Publication Number: WO 99/43660 (43) International Publication Date: 2 September 1999 (02.09.99)</p>
<p>(21) International Application Number: PCT/US99/04303 (22) International Filing Date: 26 February 1999 (26.02.99) (30) Priority Data: 60/076,023 26 February 1998 (26.02.98) US (71) Applicant (for all designated States except US): NEUROGEN CORPORATION [US/US]; 35 Northeast Industrial Road, Branford, CT 06405 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): DESIMONE, Robert, W. [US/US]; 37 Gina Drive, Durham, CT 06422 (US). MANLY, Charles [US/US]; 252 Bradley Corners Road, Madison, CT 06443 (US). (74) Agent: SARUSSI, Steven, J.; McDonnell Boehnen Hulbert & Berghoff, Suite 3200, 300 South Wacker Drive, Chicago, IL 60606 (US).</p>		<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</p>
<p>(54) Title: SUBSTITUTED 1,4-DIHYDRO-4-OXONICOTINIC CARBOXAMIDES: GABA BRAIN RECEPTOR LIGANDS</p> <div style="text-align: center;">  <p>(a)</p> </div> <p>(57) Abstract</p> <p>Disclosed are compounds of formula (a), or the pharmaceutically acceptable non-toxic salts thereof wherein: R₁ is lower alkyl; R₂ is hydrogen or lower alkyl; or R₁ and R₂ together represent a 2, 3, or 4 carbon alkylene moiety that together with the pyridone ring to which they are attached form a 5, 6 or 7 membered carbocyclic ring; and W is (un)substituted lower alkyl, aryl, arylalkyl, or heteroaryl; or W is NR₃COR₄, COR₄, CONR₃R₄ or CO₂R₄ where R₃ and R₄ are the same or different and represent hydrogen or lower alkyl, which compounds are highly selective agonists, antagonists or inverse agonists for GABA_A brain receptors or prodrugs of agonists, antagonists or inverse agonists for GABA_A brain receptors. These compounds are useful in the diagnosis and treatment of anxiety, sleep, cognitive and seizure disorders, and overdose with benzodiazepine drugs and for enhancement of alertness.</p>		

WHAT IS CLAIMED IS:

1. A compound of the formula:



or the pharmaceutically acceptable non-toxic salts thereof

5 wherein:

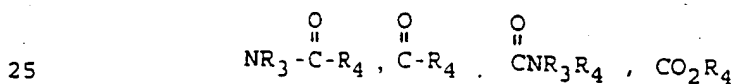
R₁ is lower alkyl;

R₂ is hydrogen or lower alkyl; or

10 R₁ and R₂ together represent a 2, 3, or 4 carbon alkylene moiety that together with the pyridone ring to which they are attached form a 5, 6, or 7 membered oxo-substituted carbocyclic ring where each carbon atom of said alkylene moiety is optionally substituted with hydroxy, halogen, C1-C6 alkyl, amino, C1-C6 alkoxy, or trifluoromethyl; and

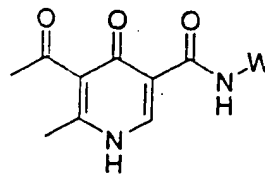
15 W is lower alkyl optionally substituted with one or two groups selected from halogen, hydroxy, lower alkoxy, amino, or mono- or dialkyl amino where each alkyl portion is independently lower alkyl; or

20 W is aryl, arylalkyl, or heteroaryl, where the ring portion of each is optionally substituted with one or two groups independently selected from halogen, trifluoromethyl, cyano, hydroxy, lower alkyl, lower alkoxy, amino, mono- or dialkylamino where each alkyl portion is lower alkyl, methylaminoalkyl where each alkyl portion is lower alkyl, or



where R₃ and R₄ are the same or different and represent hydrogen or lower alkyl.

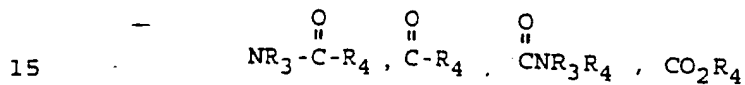
2. A compound according to claim 1 of the formula:



or the pharmaceutically acceptable non-toxic salts thereof
wherein:

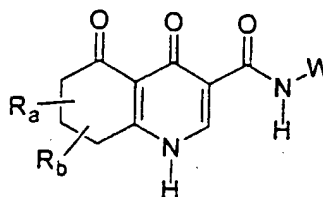
W is lower alkyl optionally substituted with one or two groups
5 selected from halogen, hydroxy, lower alkoxy, amino, or
mono- or dialkyl amino where each alkyl portion is
independently lower alkyl; or

W is aryl, arylalkyl, or heteroaryl, where the ring portion of
each is optionally substituted with one or two groups
10 independently selected from halogen, trifluoromethyl,
cyano, hydroxy, lower alkyl, lower alkoxy, amino, mono or
dialkylamino where each alkyl portion is lower alkyl,
methylaminoalkyl where each alkyl portion is lower alkyl,
or



where R₃ and R₄ are the same or different and represent
hydrogen or lower alkyl.

3. A compound according to claim 1 of the formula:



20

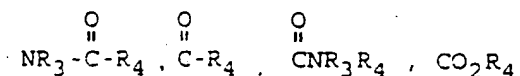
or the pharmaceutically acceptable non-toxic salts thereof
wherein:

R_a is hydrogen, halogen, hydroxy, C₁-C₆ alkyl, C₁-C₆ alkoxy,
amino, mono- or di(C₁-C₆)alkylamino, or trifluoromethyl;

25 R_b is halogen, hydroxy, C₁-C₆ alkyl, C₁-C₆ alkoxy, amino, mono-
or di(C₁-C₆)alkylamino, or trifluoromethyl;

W is lower alkyl optionally substituted with one or two groups selected from halogen, hydroxy, lower alkoxy, amino, or mono- or dialkyl amino where each alkyl portion is independently lower alkyl; or

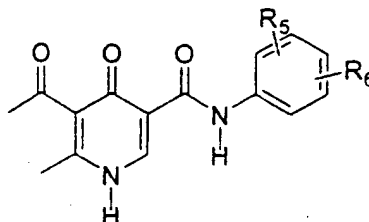
- 5 W is aryl, arylalkyl, or heteroaryl, where the ring portion of each is optionally substituted with one or two groups independently selected from halogen, trifluoromethyl, cyano, hydroxy, lower alkyl, lower alkoxy, amino, mono- or dialkylamino where each alkyl portion is lower alkyl, methylaminoalkyl where each alkyl portion is lower alkyl,
 10 or



where R₃ and R₄ are the same or different and represent hydrogen or lower alkyl.

15

4. A compound according to claim 1 of the formula:

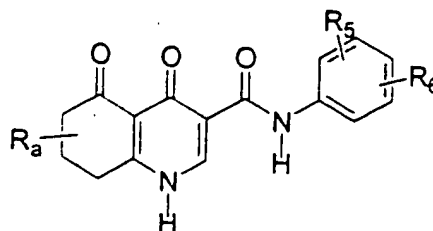


or the pharmaceutically acceptable non-toxic salts thereof
 wherein:

- 20 R₅ and R₆ are the same or different and represent hydrogen, halogen, hydroxy, lower alkyl, lower alkoxy, amino, mono or dialkylamino where each alkyl portion is lower alkyl, or methylaminoalkyl where each alkyl portion is lower alkyl.

25

5. A compound according to claim 1 of the formula:

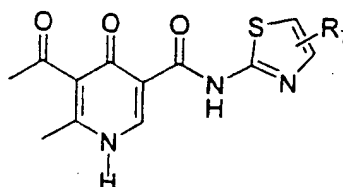


or the pharmaceutically acceptable non-toxic salts thereof wherein:

R_a is hydrogen, halogen, hydroxy, C₁-C₆ alkyl, C₁-C₆ alkoxy, amino, mono- or di(C₁-C₆)alkylamino, or trifluoromethyl;

R₅ and R₆ are the same or different and represent hydrogen, halogen, hydroxy, lower alkyl, lower alkoxy, amino, mono or dialkylamino where each alkyl portion is lower alkyl, or methylaminoalkyl where each alkyl portion is lower alkyl.

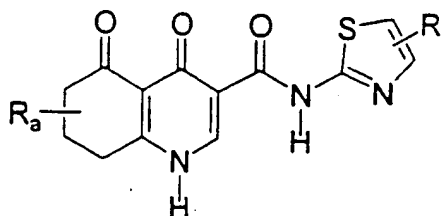
6. A compound according to claim 1 of the formula:



or the pharmaceutically acceptable non-toxic salts thereof wherein:

R₇ is hydrogen, halogen, hydroxy, lower alkyl, lower alkoxy, amino, mono or dialkylamino where each alkyl portion is lower alkyl, or methylaminoalkyl where each alkyl portion is lower alkyl.

7. A compound according to claim 1 of the formula:



5 R7 is hydrogen, halogen, hydroxy, lower alkyl, lower alkoxy, amino, mono or dialkylamino where each alkyl portion is lower alkyl, or methylaminoalkyl where each alkyl portion is lower alkyl.

CC(=O)c1c(C)c[nH]c1C(=O)NCCc2ccc(*)cc2

R₈ and R₉ are the same or different and represent hydrogen, halogen, cyano, hydroxy, lower alkyl, lower alkoxy, amino, mono or dialkylamino where each alkyl portion is lower alkyl, methylaminoalkyl where each alkyl portion is lower alkyl.

O=C1C(=O)c2c(c1)nc(C(=O)NCC3=CC=CC=C3R9)c2R_a

R₈ and R₉ are the same or different and represent hydrogen, halogen, cyano, hydroxy, lower alkyl, lower alkoxy, amino, mono or dialkylamino where each alkyl portion is

lower alkyl, methylaminoalkyl where each alkyl portion is lower alkyl.

10. A compound according to claim 1 which is N-(2-
5 fluorophenyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide.

11. A compound according to claim 1 which is N-(4-methoxyphenyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-
10 3-carboxamide.

12. A compound according to claim 1 which is N-(4-methoxy-2-pyridyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide.
15

13. A compound according to claim 1 which is N-(4-(±)-(1-methylaminoethyl)benzyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide.

14. A compound according to claim 1 which is N-(n-Butyl)-1,4,5,6,7,8-hexahydroquinoline-4,5-dione-nicotinic-3-carboxamide.
20

15. A compound according to claim 1 which is N-(4-ethoxyphenyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide.
25

16. A compound according to claim 1 which is N-(3-fluorophenyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide.
30

17. A compound according to claim 1 which is N-(2-fluoro-4-methoxyphenyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide.

18. A compound according to claim 1, which is: N-(3-tolyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide.

5

19. A compound according to claim 1 which is N-(2,4-difluorophenyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide.

10

20. A compound according to claim 1 which is N-(2,6-difluorophenyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide.

21. A compound according to claim 1 which is N-(benzyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide.

15

22. A compound according to claim 1 which is N-(2-methoxyphenyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide.

20

23. A compound according to claim 1 which is N-(3-methylaminomethylphenyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide.

25

24. A compound according to claim 1 which is N-(2-fluorobenzyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide.

25. A compound according to claim 1 which is N-(2,3-difluorobenzyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide.

30

26. A compound according to claim 1 which is N-(isoamyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide.
- 5 27. A compound according to claim 1 which is N-(4-chlorobenzyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide.
- 10 28. A compound according to claim 1 which is N-(phenyl)-1,4,5,6,7,8-hexahydroquinoline-4,5-dione-nicotinic-3-carboxamide.
- 15 29. A compound according to claim 1 which is N-(2-fluorophenyl)-1,4,5,6,7,8-hexahydroquinoline-4,5-dione-nicotinic-3-carboxamide.
- 20 30. A compound according to claim 1 which is N-(2-thiazolyl)-1,4,5,6,7,8-hexahydroquinoline-4,5-dione-nicotinic-3-carboxamide.
31. A compound according to claim 1 which is N-(benzyl)-1,4,5,6,7,8-hexahydroquinoline-4,5-dione-nicotinic-3-carboxamide.
- 25 32. A compound according to claim 1 which is N-(2-fluorobenzyl)-1,4,5,6,7,8-hexahydroquinoline-4,5-dione-nicotinic-3-carboxamide.
- 30 33. A compound according to claim 1 which is N-(4-methoxybenzyl)-1,4,5,6,7,8-hexahydroquinoline-4,5-dione-nicotinic-3-carboxamide.
34. A compound according to claim 1 which is N-(phenyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide.

35. A compound according to claim 1 which is N-(Butyl)-
1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide.

5 36. A compound according to claim 1 which is N-(2(4-
Methylthiazoleyl))-1,4-dihydro-4-oxo-5-acetyl-6-methyl
nicotinic-3-carboxamide.

10 37. A compound according to claim 1 which is N-(2-(4-
methoxy)pyridyl)-1,4,5,6,7,8-hexahydroquinoline-4,5-dione-
nicotinic-3-carboxamide.

15 38. A compound according to claim 1 which is N-(2-
thiazolyl)-1,4,5,6,7,8-hexahydroquinoline-4,5-dione-nicotinic-
3-carboxamide.